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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,836	11/10/2005	Klaus Kopka	PZ0277	2454

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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
02/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,836	KOPKA ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/10/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 9-32* is/are pending in the application.

4a) Of the above claim(s) *3,4,17,19-25 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9-16,18,26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 11/10/2009, in reply to the Office Action mailed 8/12/2009, is acknowledged and has been entered. Claims 2 and 5-8 have been cancelled. Claims 1, 3, 16, 19 and 24 have been amended. Claims 1, 3, 4 and 9-32 are pending, of which claims 3, 4, 17, 19-25 and 30-32 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1, 9-16, 18 and 26-29 are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by claim amendment.

Applicant's arguments have been fully considered but they are not persuasive, for reasons set forth hereinbelow.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 15, 16, 18 and 26-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Noe (US 6,706,723), for reasons set forth in the previous Office Action.

Applicant argues on page 12 of the Response that the claims have been amended to overcome any anticipation of Noe, and point out that Noe is silent on imaging, in particular *in vivo* imaging agents. Applicant argues that the art in the field of radiopharmaceutical imaging agents could have no motivation to use Noe as suggested by the Examiner, since Noe is silent on imaging. Applicant further argues that Noe teaches instead the use of ^{3}H or ^{14}C labels for "drug and/or substrate tissue distribution assays". Applicant argues that Noe teaches that ^{3}H or ^{14}C are particularly preferred labels Noe teaches away from the subject matter of the present claims.

This is not found to be persuasive. In response to applicant's argument that Noe does not intend his compounds for in vivo imaging, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Further, it is noted that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Applicant's arguments that Noe teaches that ^{3}H or ^{14}C are particularly preferred, and that Noe teaches away from the subject matter of the present claims have been

fully considered. However, it is deemed that the reference does not reach the level of a teaching away from labeling with ^{18}F, as suggested by Applicant. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See MPEP 2145. In the instant case, the Noe reference merely teaches that ^{3}H and ^{14}C are preferred, but does not teach away from ^{18}F. In addition, non-preferred embodiments constitute prior art. MPEP 2123.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9-16, 18 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grams *et al.* (*Biol. Chem.*, 2001, 382, p. 1277-1285) in view of Noe

(US 6,706,723), further in view of Carpenter *et al*. (US 6,656,448) and Mobashery *et al.* (US 6,703,415), for reasons set forth in the previous Office Action.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Grams *et al.* (*Biol. Chem.*, 2001, 382, p. 1277-1285) in view of Noe (US 6,706,723), further in view of Carpenter *et al*. (US 6,656,448) and Mobashery *et al.* (US 6,703,415), as applied to claims 1, 9-16, 18 and 26-28 above, in further view of Luthra *et al.* (US 7,115,249), as set forth in the previous Office Action.

Applicant argues on pages 12-15 of the Response that Noe is silent on imaging, in particular *in vivo* imaging agents, and that the person skilled in the art in the field of radiopharmaceutical imaging agents could have no motivation to use Noe as suggested by the Examiner, since Noe is silent on imaging. Applicant asserts that Noe teaches instead the use of ^{3}H or ^{14}C labels for "drug and/or substrate tissue distribution assays," preferably ^{3}H or ^{14}C, and contends that Noe teaches away from the subject matter of the present claims. Applicant argues that Noe does not teach labeling at the 5 postiion. Applicant asserts that Noe itself clearly states that any position of the barbituric acid can be isotopically labeled. Since Noe includes isotopes of H, C, N, O, P, F and Cl, Applicants contend that ascribing any teaching to Noe on selecting the 5-position for radiolabelling involves the invalid application of hindsight, based on the teaching of the present invention. Applicant further argues that whilst Noe does mention the possibility of isotopic labeling, the person of skill in the art would know that these fall into various

categories including non-radioactive and radioactive, and that of those cited by Noe, only 18F is suited for in vivo radiopharmaceutical imaging, and that there is no basis to select 18F over the many other isotopes taught.

This is not found to be persuasive. In response to applicant's argument that Noe does not intend his compounds for in vivo imaging, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Further, it is noted that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Applicant's arguments that Noe teaches that ^{3}H or ^{14}C are particularly preferred, and that Noe teaches away from the subject matter of the present claims have been fully considered. However, it is deemed that the reference does not reach the level of a teaching away from labeling with ^{18}F, as suggested by Applicant. A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). Furthermore, "the prior art's mere disclosure of more than one

alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See MPEP 2145. In the instant case, the Noe reference merely teaches that ^{3}H and ^{14}C are preferred, but does not teach away from ^{18}F. In addition, non-preferred embodiments constitute prior art. MPEP 2123. With respect to labeling at the five position, the only position of barbituric acid at which Noe provides a fluorine atom is at the 5-position. Thus it would be logical that when a radiolabeled fluorine is incorporated, it would be at the 5-position; and when fluorine is present on a given compound one would have had reasonable motivation to include ^{19}F, as that is the only radioactive fluorine isotope taught by Noe.

Applicant further argues on pages 15-16 of the Response that Grams is silent on radiolabelled barbituric acid derivatives for PET imaging [emphasis added]. Hence, Grams is necessarily silent on which isotopes to attach and where. Applicant asserts that Carpenter and Mobashery relate to MMPs which are structurally completely unrelated to barbituric acid derivatives. They too, can therefore provide no teaching on the site of radioisotope labeling to provide an *in vivo* imaging agent when the MMPi is a barbituric acid derivative. As argued above, Noe does not provide this teaching either. Consequently, no combination of Grams/Noe/Carpenter/Mobashery can provide the subject matter of present revised claim 1. Finally, Applicants contend that any obviousness rejection which relies on the combination of 4 references is fundamentally flawed, since it demonstrates an invalid piecemeal approach wherein various features of

the claims are identified in multiple prior art documents. Applicants contend that whilst motivation to combine could potentially exist for two documents, it is unrealistic for four.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the compounds disclosed cited references are functionally equivalent as MMP inhibitors. One of ordinary skill would have been capable of including a radionuclide on the compounds of Gram, described as a potent MMP inhibitor, since Carpenter and Mobashery teach the desirability of using an MMP inhibitor linked to radioisotopes which are known to be useful for imaging by gamma scintigraphy or PET, such as detecting and monitoring the degree of extracellular matrix degeneration in CHF, atherosclerosis, and other degenerative disease processes. In the instant case, the cited references are all directed to MMP inhibitors. It would have been obvious to one of ordinary skill in the art to invention to provide ^{18}F labels on the pyrimidine-2,4,6-trione metalloproteinase inhibitor compounds of Grams for the purpose of preparing imaging agents targeted to one or more MMP's, which would be very useful for detecting and monitoring the degree of extracellular matrix degradation in CHF, atherosclerosis and other degradative disease processes, as shown by Carpenter and Mobashery for other known MMP inhibitor compounds. One would have been motivated to do so because Carpenter and Mobashery teach that it is well known in the art to radiolabel MMP inhibitor compounds with radioisotopes which are known to be useful

for imaging by positron emission tomography (PET), such as ^{18}F, for detection and localization of MMP and diseases associated therewith, and because Grams teaches that his compounds are more specific than other known MMP inhibitors. One would have had a reasonable expectation of success in doing so because Noe teaches that structurally similar pyrimidine-2,4,6-trione metalloproteinase inhibitors can be isotopically labeled, including using ^{18}F, which can generally be prepared by carrying out the procedures disclosed in the schemes and/or examples and preparations, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. In response to arguments regarding the number of references, see MPEP 2145. Reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention.

Conclusion

No claims are allowed at this time.

Although Applicant's arguments as set forth in the aforementioned Response have been fully considered, they are deemed unpersuasive. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS